

Rhodium(III)-catalyzed intramolecular annulations involving amide-directed C–H activations: synthetic scope and mechanistic studies

Noelia Quiñones, Andrés Seoane, Rebeca García-Fandiño, Jose Luis Mascareñas and Moisés Gulías

Accepted Manuscript

How to cite:

Quiñones, N., Seoane, A., García-Fandiño, R., Mascareñas, J., & Gulías, M. (2013). Rhodium(iii)-catalyzed intramolecular annulations involving amide-directed C–H activations: synthetic scope and mechanistic studies. *Chem. Sci.*, 4, 2874-2879. doi: 10.1039/c3sc51078f

Copyright information:

© The Royal Society of Chemistry 2013

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Rhodium (III)-catalyzed intramolecular annulations involving amide-directed C-H activations: synthetic scope and mechanistic studies

Noelia Quiñones, Andrés Seoane, Rebeca García-Fandiño, Jose Luis Mascareñas* and Moisés Gulías*^a

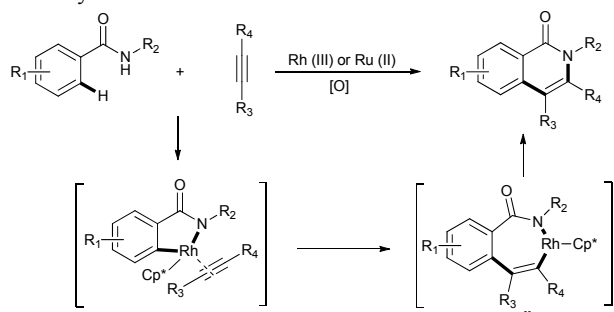
Received (in XXX, XXX) Xth XXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXX 20XX

DOI: 10.1039/b000000x

Alkyne tethered benzamides undergo rhodium(III)-catalyzed intramolecular annulations to give tricyclic isoquinoline derivatives in good yields. DFT calculations suggest that the reaction mechanism involves a migratory insertion of the alkyne into the rhodium-nitrogen bond of the rhodacycle intermediate that results from the initial C-H activation. This contrasts with the pathway proposed for intermolecular cases, which considers an insertion into the rhodium-carbon instead of the rhodium-nitrogen bond. The annulation is also effective with acrylamides; and, while anilides fail to participate in the process, naphthylamides do undergo the intramolecular annulation, albeit the chemoselectivity is different than for the intermolecular reactions.

Introduction

In recent years there has been a burst on the development of synthetic transformations relying on transition-metal catalyzed C-H bond activation processes.¹ These reactions are particularly appealing in terms of simplicity and atom economy, as they can be directly performed on readily available, non-activated precursors. Although most transformations so far developed consist of cross-coupling reactions,² there have been an increasing number of reports on C-H activation/annulation processes.³ These strategies represent a powerful alternative to classical cycloadditions of unsaturated substrates.⁴ In this regard, it has been shown that benzamides participate in formal intermolecular (4+2) annulations with different alkynes when treated with Rh(III)⁵ or Ru(II)⁶ catalysts in the presence of external oxidants. Mechanistically, these annulations have been explained in terms of an initial N-H/C-H activation to generate intermediate **I**, followed by carbometallation leading to the seven-membered intermediate **II**, which upon reductive elimination yields the isoquinolone products (Scheme 1).⁷ Using N-alkoxybenzamides the external oxidant is not needed.⁸



Scheme 1 Mechanistic proposal for intermolecular reactions of benzamides and alkynes.

As in classical cycloadditions, it would be highly desirable to add the bonus of intramolecularity to this C-H activation/annulation process. This could be readily achieved by tethering the alkyne component to the nitrogen of the amide (Figure 1). The annulation of the resulting substrates would allow a direct assembly of interesting tricyclic isoquinolines, a type of skeletons which form the basic core of a large variety of natural products.

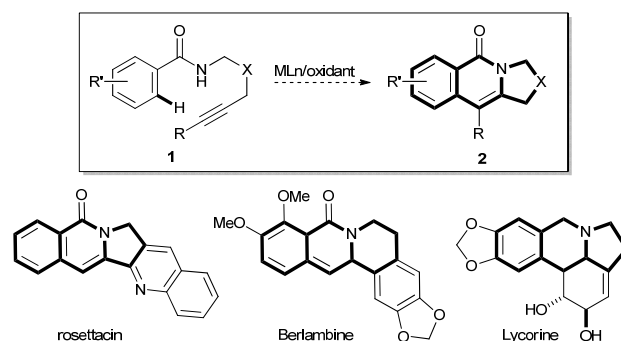


Figure 1 Some examples of natural products with a tricyclic isoquinoline core.

Although translation of the benzamide annulation chemistry to intramolecular cases might appear obvious, a quick inspection of the hypothetical reaction mechanism raises serious doubts on the viability of the reaction, as it would require the generation of strained bridged systems like **III** (Figure 2). Alternatively, and although it has not been generally considered in intermolecular cases,^{6c} the reaction might involve a migratory insertion of the alkyne into the rhodium-nitrogen instead of the rhodium-carbon bond of the rhodacycle, leading to the intermediate **IV**. Given this mechanistic uncertainty, and considering the synthetic relevance and methodological novelty of the intramolecular processes, we decided to explore the Rh-catalyzed cycloaddition of N-alkynylbenzamides.

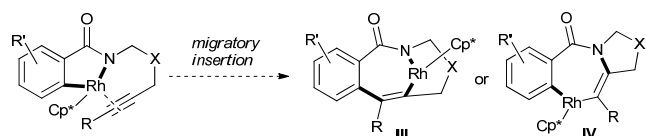
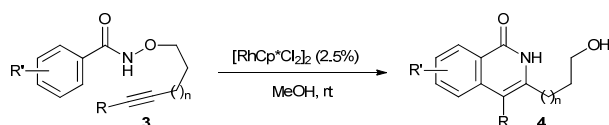


Figure 2 Two plausible intermediates resulting from a metal-carbon or a metal-nitrogen migratory insertion.

While our research was ongoing, Park and coworkers reported reaction of substrates **3**, in which the alkyne is connected to the amide through an N-O linker (Scheme 2).⁹ The process can be considered intramolecular, however the N-O bond is cleaved during the reaction, and therefore the preparation of tricyclic isoquinoline products requires additional steps. In consonance with previous mechanistic hypothesis for the intermolecular cases, the authors suggest that the annulation involves a carbometallation step to give Rh-bridged intermediates of type **III**.



Scheme 2 Annulation of benzamides reported by Park.

Herein we demonstrate that benzamides (and acrylamides)¹⁰ equipped with carbon-tethered alkynes undergo the intramolecular cycloaddition in good yields. We present DFT studies that support a reaction mechanism involving the formation of intermediates of type **IV** over the alternative bridged systems **III**. We also demonstrate that a similar tethering of the alkynes to anilides or naphthanilides provide different outcomes than in the intermolecular reactions.

Results and discussion

Initially we studied the reaction of substrate **1a** with $[\text{Cp}^*\text{RhCl}_2]_2$ under different conditions. As shown in the Table 1, heating a mixture of **1a** with this catalyst and $\text{Cu}(\text{OAc})_2$, at 110 °C in toluene, leads to the desired tricyclic product **2a**.

Table 1 Screening of the reaction conditions.^a

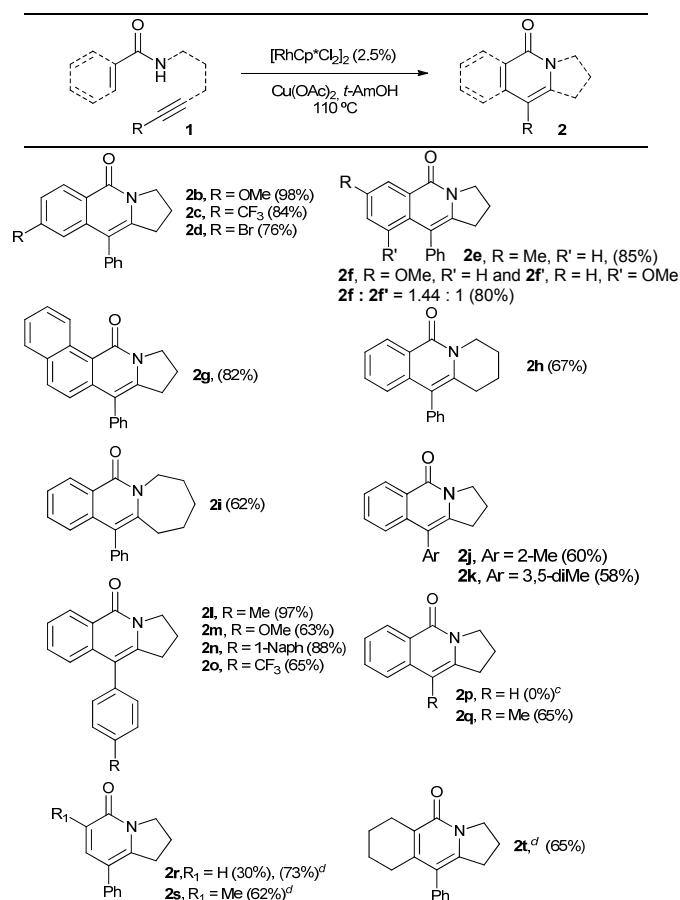
Entry	Catalyst	Oxidant	Solvent	Yield ^b
1	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	Toluene	57
2	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	98
3	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	acetone	35
4	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	DMF	58
5	$[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	– ^c
6	$[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	– ^c
7	$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	50
8	$[\text{Cp}^*\text{IrCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	<i>t</i> -AmOH	23
9	$\text{Pd}(\text{OAc})_2$	Benzoquinone	<i>t</i> -AmOH ^d	– ^e

^a Reaction conditions: **1a** (0.25 mmol), catalyst (2.5 mol%), oxidant (0.5 mmol), solvent (2.0 mL), 110 °C, 12 h. ^b isolated yield ^c Complex mixture of products. ^d 0.15 equiv. of *p*-TsOH·H₂O were added. ^e The starting material was mostly recovered.

The reaction is more efficient when *t*-AmOH is used as solvent, which allowed to obtain **2a** in 98% of yield (entry 2). Other solvents such as DMF or acetone were less effective, leading to lower yields of the products. Curiously, cationic catalysts $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$ ^{10b} or $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ ^{5b} which had been reported to work in intermolecular cases, failed to give the cycloadducts (entries 5 and 6). We also checked the performance of other metals; thus, whereas $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ works, although not full conversion is achieved with 2.5 mol% of the catalyst (entry 7), an analogous iridium complex $[\text{Cp}^*\text{IrCl}_2]_2$ led to poor conversions (entry 8). We also tested $\text{Pd}(\text{OAc})_2$ in combination with *p*-TsOH, but in this case we recovered the starting material (entry 9).

With the optimized conditions in hand, we next examined the scope of the reaction with other substrates (Table 2).

Table 2 Scope of the intramolecular cycloaddition of benzamides or acrylamides and alkynes.^{a,b}



^a Reaction conditions: **1** (0.25 mmol), catalyst (2.5 mol%), $\text{Cu}(\text{OAc})_2$ (0.5 mmol), *t*-AmOH (2.0 mL), 110 °C. ^b Isolated yields. ^c The starting material was mostly recovered. ^d 1.2 equiv. of CsOAc were added.

As shown in the table, the reaction tolerates electronically distinct substituents in the aryl moiety of the benzamide; therefore good yields could be obtained with either electron-rich (**1b**) or electron poor substituents such as trifluoromethyl (**1c**). The reaction is compatible with the presence of bromide atoms in the benzene ring, leading to products (**2d**) amenable for subsequent modifications.

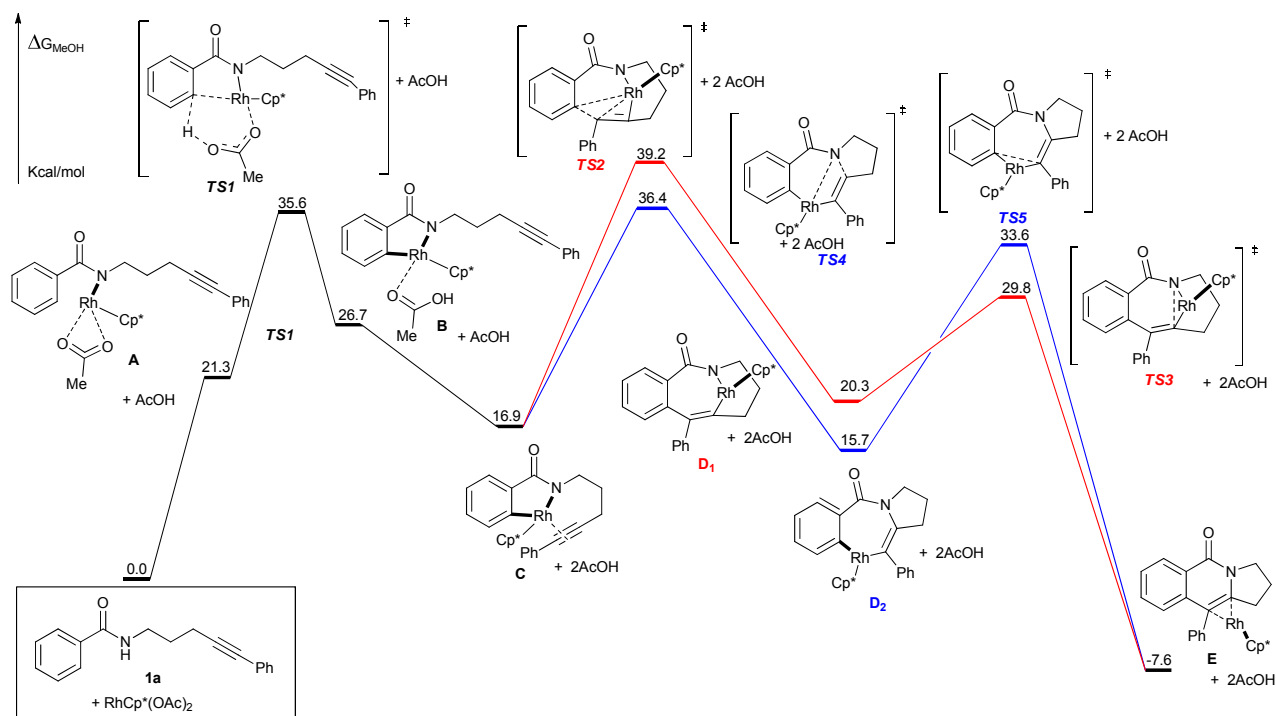


Figure 3 Mechanistic pathways investigated by DFT calculations for standard substrate **1a**.

We also tested the reaction in substrates containing a methyl (**1e**) or methoxy (**1f**) group in the *meta* position of the phenyl ring.

Both gave good yields of the cycloadducts, but while the reaction of **1e** was totally selective to give **2e**, the methoxy derivative led to a mixture of regioisomers. Naphthylbenzamides are also productive substrates, leading to interesting tetracyclic adducts like **2g** (82% yield).

Substrates featuring a longer carbon tether between the benzamide and the alkyne also participate in the cycloaddition, leading to products containing either a six- (**2h**, 67% yield) or a seven-membered ring (**2i**, 62% yield).

The cycloaddition also tolerates a great variety of groups in the phenyl substituent of the alkyne, including electron donating moieties, like methyls, methoxy, or naphthyls (**1j-1n**), or electron withdrawing substitutions like trifluoromethyl (**1o**). Finally, although substrates bearing a terminal alkyne led to recovery of most of the starting material (**1p**), the reaction works efficiently with alkyl substituted alkynes, as shown for the case of **1q** (65%). Interestingly, we also found that the cycloaddition also works with several alkyne-tethered acrylamides, to produce interesting indolizinones **2r-t** in good yields. In this case, the reaction was more efficient when carried out in presence of 1.2 equiv. of CsOAc.¹¹

The above results confirm that the Rh(III)-catalyzed intramolecular annulation of *N*-alkynyl tethered benzamides is not only viable, but a quite robust and synthetically attractive reaction. The quest on whether the reaction proceeds through a N- or a C-metallation step was now in the air (Figure 2). In order to shed light into this issue, we decided to do a computational study of the reaction mechanism using DFT calculations,¹² and compare the activation energies required to make intermediates of type **III** or **IV**. Therefore we

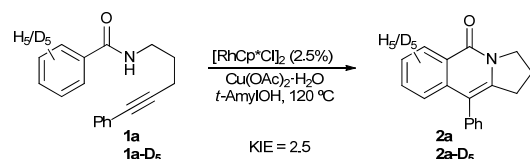
The study was accomplished using Cp*Rh(OAc)₂ as active

catalytic species, which would be presumably formed by dissociation of the rhodium dimer precatalyst into a coordinatively unsaturated monomer, followed by ligand exchange with acetates.¹³ Therefore, the catalytic cycle starts when Cp*Rh(OAc)₂ coordinates to the starting material **1a**, with concomitant loss of acetic acid (Figure 3). Next, a C-H bond cleavage would occur via a concerted metallation-deprotonation (CMD) transition state (**TS1**), leading to intermediate **B**, in which acetic acid is still bound to rhodium.¹⁴ CMD **TS1** exhibits a relative Gibbs free energy of 35.6 kcal·mol⁻¹, and structural features very similar to those reported for similar processes in intermolecular reactions (the C-H and O-H distances for the proton transfer are 1.33 and 1.31 Å, respectively, and the Rh-C distance is 2.22 Å).^{7b} At this point, dissociation of the acetic acid ligand and coordination of the alkyne to Rh(III) gives intermediate **C**,¹⁵ which could now evolve either through a C- or N-metallation step. The first possibility, which is usually invoked in the intermolecular cases, involves insertion of the alkyne in the Rh-C bond to give intermediate **D1**, and occurs via **TS2** (pathway 1, in red, Gibbs energy: 39.2 kcal·mol⁻¹). Reductive elimination via **TS3** (ΔG: 29.8 kcal·mol⁻¹) delivers the products and a Rh(I) complex. It is interesting to note that the C-Rh-N angle in **D1** (76.5°) is not very different to that in **C** (79.3°) or **TS2** (74.2°), which suggests a relatively comfortable transformation despite the generation of a presumably tense bridged system. This tension seems to be responsible of the relatively low barrier for the ensuing reductive elimination.

Importantly, the pathway involving an N-metallation via **TS4** to give intermediate **D2** (pathway 2, in blue), is 2.8 kcal·mol⁻¹ less costly than the above route via **TS2**. The distances of the bonds being broken and formed in **TS4** are relatively large (Rh-N: 2.148 Å, and N-alkyne: 2.127 Å, respectively), suggesting an early TS. The reductive elimination steps, either through **TS3** or **TS5**, lead to the product and Rh(I) which is subsequently reoxidized to Rh(III) by Cu(OAc)₂.

We have also calculated the potential energy surface for a substrate containing one additional methylene group between the amide and the alkyne. The resulting computational data indicate that there is a drop in the energies of the migratory insertion step, but the insertion of the alkyne into the N-Rh bond is still favoured by 1.8 kcal·mol⁻¹ (see the supporting information).

All the above calculations suggest that, as might be expected, the formation of a Rh-bridged structure is penalized, and pathway 2, is slightly more favourable. This might be also the case in the annulation reaction described by Park and coworkers (scheme 2). Consistent with the computational results, which suggest that the C-H cleavage is a turnover limiting step, we found a noticeably deuterium kinetic isotope effect (DKIE: 2.5), as deduced from the comparison of initial rates for the reaction of precursors **1a** and **1a-D₅** (scheme 3).



Scheme 3 DKIE measurements

Since the above computational data suggest that the migratory insertion of the alkyne onto the Rh-N is preferred over the carbometallation process, we were curious to know the viability of a similar pathway for the intermolecular cases. We therefore carried out similar DFT calculations, which indicated that the N-metallation is slightly more costly, but the differences in activation barriers are not high enough to fully discard this pathway (figure 4).

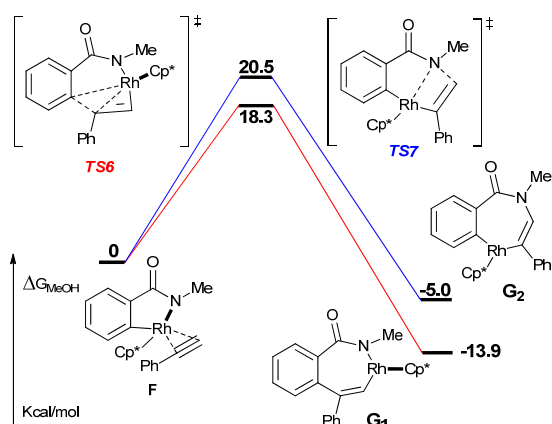
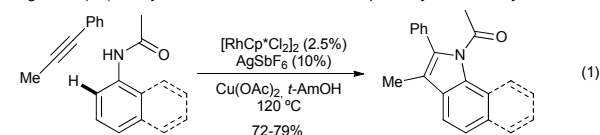


Figure 4 Relative energy values of the migratory insertion pathways for the intermolecular reaction.

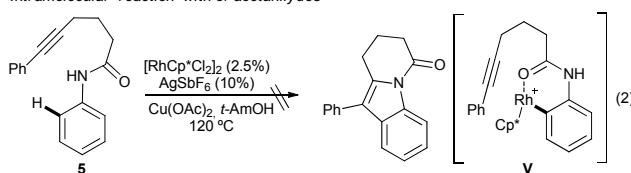
Intermolecular metal-catalysed annulations to alkynes relying on C-H activation processes have also been studied with anilides instead of benzamides. In this case the process formally consists of a (3+2) cycloaddition, and leads to indole skeletons (equation 1, scheme 4).¹⁶ Hypothetically, this reaction might also be implemented in an intramolecular manner by using N-tethered alkynes. However, treatment of substrate **5** with [RhCp*Cl₂]₂/AgSbF₆, conditions previously used in intermolecular cases, led to decomposition of the starting material (equation 2, scheme 4).¹⁷ Although at a first sight this could appear surprising, the lack of reactivity can be explained by invoking the formation of a

death intermediate **V**, in which the alkyne is not able to coordinate appropriately to the metal for geometrical reasons, and therefore cannot undergo the required migratory insertion.¹⁸ Interestingly, in the case of naphthanilide **6** (equation 3), the annulation reaction does take place, but not to give the indole product, but an alternative adduct (**7**), formally arising from a (4+2) annulation. The formation of this product can be easily explained through the formation of metallacycle intermediate **VI**, which in this case is geometrically accessible.

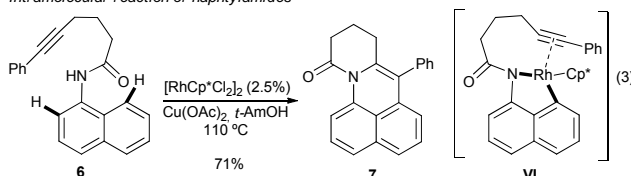
Fagnou Rh(III)-catalyzed reaction of anilides and naphthanilides with alkynes



Intramolecular reaction with acetanilides



Intramolecular reaction of naphthylamides



Scheme 4 C-H/N-H activation/cycloaddition of acetanilides and naphthylamides.

These examples with anilides confirm that translating intermolecular annulations based on C-H activation protocols to the intramolecular arena is not as straight as in the case of standard metal-catalyzed cycloadditions involving π -unsaturated substrates.

Conclusions

In summary, we have demonstrated that benzamides or acrylamides bearing N-tethered alkynes undergo rhodium(III)-catalyzed intramolecular annulations to produce interesting polycyclic isoquinolones or indolizinones in a straightforward manner. DFT calculations suggest that the migratory insertion of the alkyne into rhodacycle resulting from the initial CH-activation step takes place into the Rh-N instead of the Rh-C bond. We have also found that while anilides do not react, naphthylamides undergo a formal (4+2) cycloaddition to amide tethered alkynes.

Acknowledgements

This work was supported by the Marie Curie Foundation (PERG06-GA-2009-256568), Xunta de Galicia (EM 2012/117, GRC2010/12) the Spanish MINECO (SAF2010-20822-02), Consolider Ingenio 2010 (CSD2007-00006) and the European Social Fund. M.G. acknowledges Xunta de Galicia for financial support from Parga Pondal program and R.G.F. thanks the Spanish Ministry of Education and Science for financial support

from the program Juan de la Cierva. All calculations were carried out on the Centro de Supercomputación de Galicia (CESGA).

Notes and references

^a Departamento de Química Orgánica, Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), and Unidad Asociada al CSIC. Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain. Fax: +34 981 595012; Tel: +34 881815760; E-mail: moises.gulias@usc.es; joseluis.mascarenas@usc.es.

[†] Electronic Supplementary Information (ESI) available: [[experimental procedures and characterization data]. See DOI: 10.1039/b000000x/

- For selected reviews on C-H activation, see: (a) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.* 2009, **48**, 9792-9826; (b) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.* 2009, **38**, 3242-3272; (c) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.* 2010, **39**, 712-733; (d) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.* 2010, **110**, 624-655; (e) T. W. Lyons and M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147-1169; (f) C. S. Yeung and V. M. Dong, *Chem. Rev.* 2011, **111**, 1215-1292; (g) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.* 2011, **40**, 1885-1898; (g) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.* 2011, **40**, 4740-4761; (h) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.* 2011, **40**, 5068-5083; (i) D. Y. K. Chen and S. W. Youn, *Chem. Eur. J.*, 2012, **18**, 9452-9474; (j) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed.* 2012, **51**, 8960-9009.
- For a comprehensive review on C-H activation/cross-coupling processes with Pd catalysts, see: X. Chen, K. M. Engle, D.-H. Wang, and J.-Q. Yu *Angew. Chem. Int. Ed.* 2009, **48**, 5094-5115.
- For selective publications on C-H activation/annulation see: (a) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato and M. Miura, *J. Org. Chem.* 2011, **76**, 13-24; (b) F. Wang, G. Song, Z. Du and X. Li, *J. Org. Chem.* 2011, **76**, 2926-2932; (c) P. C. Too, T. Noji, Y. J. Lim, X. Li and S. Chiba, *Synlett* 2011, 2789-2794; (d) Y.-F. Wang, K. K. Toh, J.-Y. Lee and S. Chiba, *Angew. Chem. Int. Ed.* 2011, **50**, 5927-5931; (e) G. Song, X. Gong and X. Li, *J. Org. Chem.* 2011, **76**, 7583-7589; (f) X. Wei, M. Zhao, Z. Du and X. Li, *Org. Lett.* 2011, **13**, 4636-4639; (g) T.-C. Wu, C.-C. Tai, H.-C. Tiao, Y.-T. Chang, C. C. Liu, C.-H. Li, C.-H. Huang, M.-Y. Kuo and Y.-T. Wu, *Chem. Eur. J.*, 2011, **17**, 7220-7227; (h) X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia and X. Li, *Adv. Synth. Cat.* 2011, **353**, 719-723; (i) L. Ackermann, J. Pospech, K. Graczyk and K. Rauch, *Org. Lett.* 2012, **14**, 930-933; (j) L. Ackermann, L. H. Wang and A. V. Lygin, *Chem. Sci.* 2012, **3**, 177-180; (k) S. Duttwyler, C. Lu, A. L. Rheingold, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.* 2012, **134**, 4064-4067; (l) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi and M. Miura, *Org. Lett.* 2012, **14**, 2058-2061; (m) T. K. Hyster, L. Knorr, T. R. Ward and T. Rovis, *Science* 2012, **338**, 500-503; (n) C. Kornhaas, J. Li and L. Ackermann, *J. Org. Chem.* 2012, **77**, 9190-9198; (o) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem. Int. Ed.* 2012, **51**, 3948-3952; (p) W. Ma, K. Graczyk and L. Ackermann, *Org. Lett.* 2012, **14**, 6318-6321. (q) R. M. Martin, R. G. Bergman and J. A. Ellman, *J. Org. Chem.* 2012, **77**, 2501-2507; (r) M. V. Pham, B. Ye and N. Cramer, *Angew. Chem. Int. Ed.* 2012, **51**, 10610-10614; (s) Z. Shi, C. Tang and N. Jiao, *Adv. Synth. Cat.* 2012, **354**, 2695-2700; (t) V. S. Thirunavukkarasu, M. Donati and L. Ackermann, *Org. Lett.* 2012, **14**, 3416-3419; (u) H. Wang and F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 7318-7322; (v) M. V. Pham, B. Ye and N. Cramer, *Angew. Chem. Int. Ed.* 2012, **51**, 10610-10614; (w) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.* 2012, **134**, 19592-19595; (x) B. Ye and N. Cramer, *Science* 2012, **338**, 504-506; (y) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem. Int. Ed.* 2013, **52**, 629-633. For a review with some early contributions with Rh see: (z) T. Satoh and M. Miura, *Chem. Eur. J.* 2010, **16**, 11212-11222.
- For selected reviews of metal-catalyzed cycloadditions see: (a) M. Lautens, W. Klute, and W. Tam, *Chem. Rev.* 1996, **96**, 49-92; (b) N. E. Schore, *Chem. Rev.* 1988, **88**, 1081-1119; (c) M. Gulias, F. Lopez and J. L. Mascarenas, *Pure Appl. Chem.* 2011, **83**, 495-506; (d) F. Lopez and J. L. Mascarenas, *Beilstein J. Org. Chem.* 2011, **7**, 1075-1094.
- (a) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.* 2010, **39**, 744-746; (b) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.* 2010, **132**, 10565-10569; (c) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.* 2010, **75**, 7487-7490.
- (a) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem. Int. Ed.*, 2011, **50**, 6379-6382. (b) L. Ackermann, A. V. Lygin and N. Hofmann, *Org. Lett.* 2011, **13**, 3278-3281. (c) B. Li, H. Feng, S. Xu and B. Wang, *Chem. Eur. J.* 2011, **17**, 12573-12577.
- For a detailed study on intermolecular reactions with alkynes, including DFT calculations, see: (a) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.* 2011, **133**, 6449-6457. For a recent study on the intermolecular reaction of benzamides with alkenes see: (b) L. Xu, Q. Zhu, G. Huang, B. Cheng and Y. Xia, *J. Org. Chem.* 2011, **77**, 3017-3024.
- (a) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.* 2010, **132**, 6908-6909; (b) L. Ackermann and S. Fenner, *Org. Lett.* 2011, **13**, 6548-6551; (c) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.* 2012, **134**, 19592-19595 (d) M. Deponti, S. I. Kozhushkov, D. S. Yufit and L. Ackermann, *Org. Biomol. Chem.* 2013, **11**, 142-148.
- X. Xu, Y. Liu and C.-M. Park, *Angew. Chem. Int. Ed.* 2012, **51**, 9372-9376.
- For examples of intermolecular cycloadditions of acrylamides: (a) Y. Su, M. Zhao, K. Han, G. Song and X. Li, *Org. Lett.* 2010, **12**, 5462-5465; (b) T. K. Hyster and T. Rovis, *Chem. Sci.* 2011, **2**, 1606-1610.
- The presence of CsOAc is probably favouring the first step of the cycle, involving a carboxylate assistance. (a) D. Lapointe and K. Fagnou, *Chem. Lett.* 2010, **39**, 1119; (b) L. Ackermann, *Chem. Rev.* 2011, **111**, 1315-1345.
- Gas-phase calculations were performed with Gaussian03 and Gaussian09 at DFT level. The geometries of all complexes here reported were optimized using the B3LYP hybrid functional. Optimizations were carried out using the standard 6-31G (d) basis set for C, H, O, and N. The LANL2DZ basis set was used for Rh. Single-point PCM calculations (MeOH) for stationary points were performed using the 6-311+G-(2df,2p) basis set for C,H,O and N, and SDD for Rh. Electronic energy values calculated with the smaller basis set have been corrected using the residual energy at the zero point vibrational energy (ZPE).
- The formation of Cp*Rh(OAc)₂ as active species is generally accepted on literature.
- Preliminary calculations were also conducted for the CMD step with the alkyne coordinated to Rh(III) and the acetate monocoordinated. The energy found was a very high and consequently this pathway was ruled out.
- Two different conformations were found for intermediate C: the one with a lower energy shows a "pseudo-chair" conformation and evolves through **TS2**. The other one, with a "pseudo-boat" conformation, reacts through **TS4**. See supporting information for more information.
- For selected references of indole synthesis via C-H/N-H activation and annulation with Rh(III) catalysts see: (a) D. R. Stuart, M. G. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.* 2008, **130**, 16474-16475; (b) R. Bernini, G. Fabrizi, A. Sferrazza and S. Cacchi, *Angew. Chem. Int. Ed.*, 2009, **48**, 8078-8081; (c) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Chem. Soc.* 2010, **132**, 18326-18339; (d) L. Ackermann and A. V. Lygin, *Org. Lett.*, 2012, **14**, 764-767. (e) M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem. Int. Ed.* 2011, **50**, 1338-1341; (f) F. Zhou, X. Han and X. Lu, *Tetrahedron Letters*, 2011, **52**, 4681-4685.
- Same results were obtained under conditions standard for benzamides, even in the presence of CsOAc.

-
- 18 Addition of an external alkyne to this reaction led to formation of the indole product arising from the intermolecular reaction, although in moderate yield.